Engineering Remotely Controllable CAR T Cells for Cancer Immunotherapy

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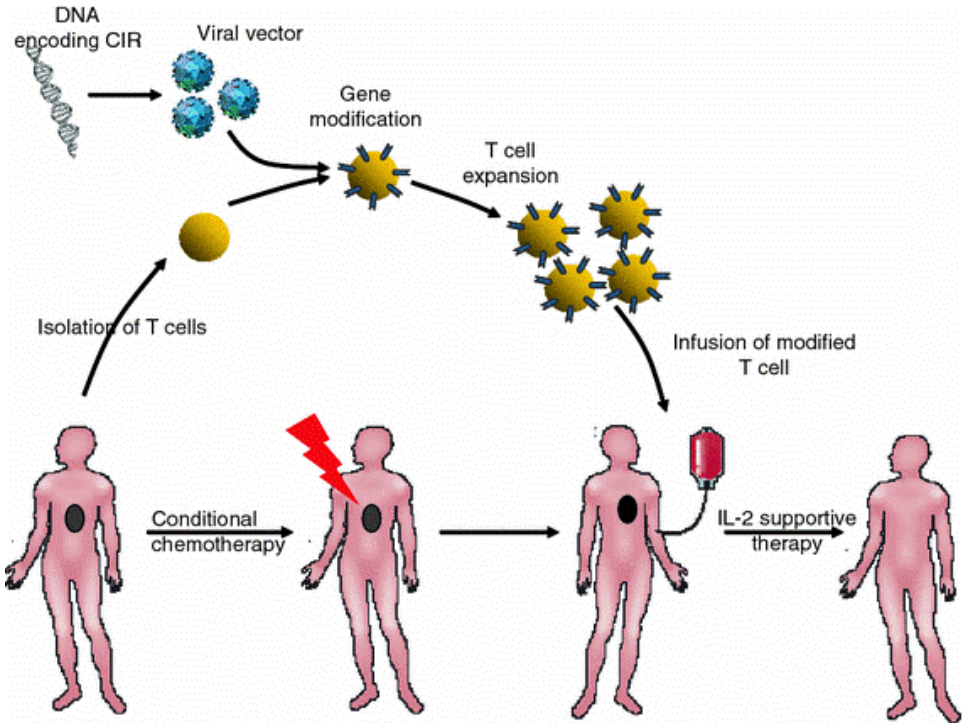
Outline

1. **The engineering of Light-controllable CAR T cells for cancer immunotherapy**
2. **The engineering of Ultrasound-controllable CAR T cells for therapeutics**

The Genetic Engineering of Chimeric Antigen Receptor (CAR) T cells



CAR T cell therapy is becoming a paradigm-shifting therapeutic approach for cancer treatment. However, major challenges remain before CAR-based immunotherapy can become widely adopted, such as cytokine storm, on target off tumor toxicity.

Different approaches have been developed to **engineer controllable CAR T cells via synthetic biology** (Kloss CC, et al, Sadelain M. Nat Biotechnol. 2013; Wu CY, et al Lim WA. Science. 2015; Roybal KT, Lim WA. Cell. 2016; Chang ZL, et al Chen YY. Nat Chem Biol. 2018; Cho JH, Collins JJ, Wong WW. Cell. 2018; Abedi MH, et al, Shapiro MG.ACS Synth Biol. 2020)

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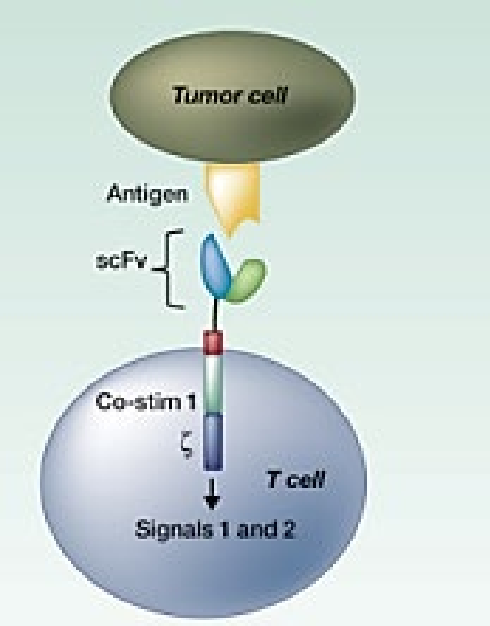
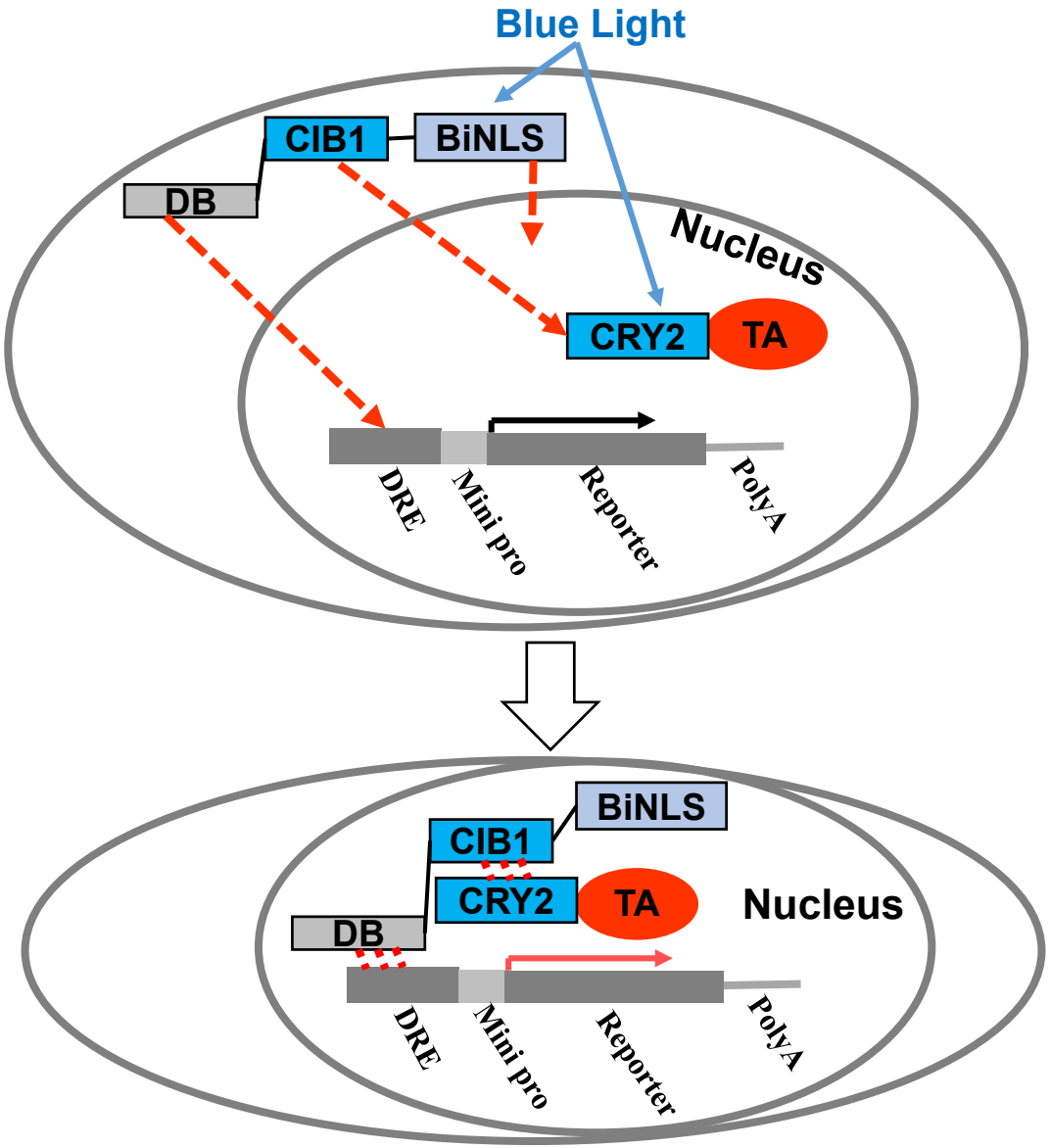
A photoactivation system for the control of gene expressions in mammalian cells

CAR T cancer immunotherapy

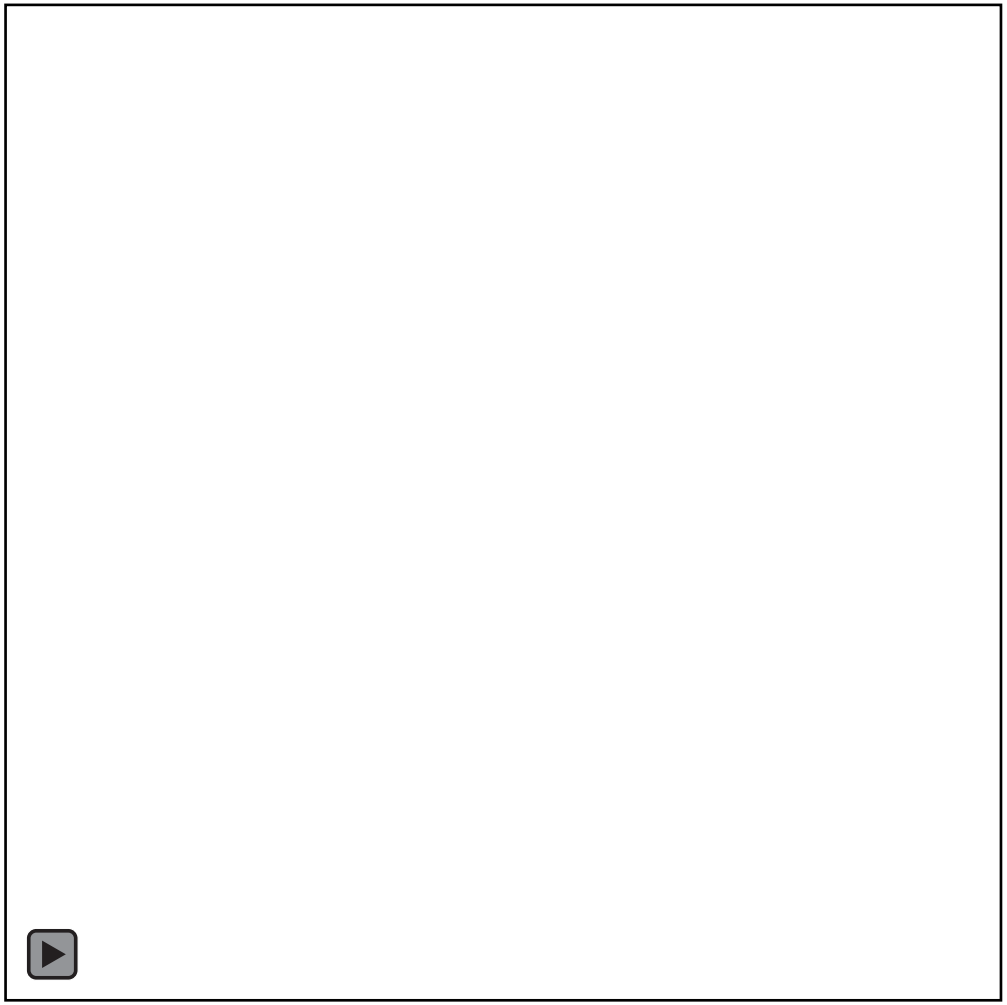


A major problem:
On target, off tumor toxicity

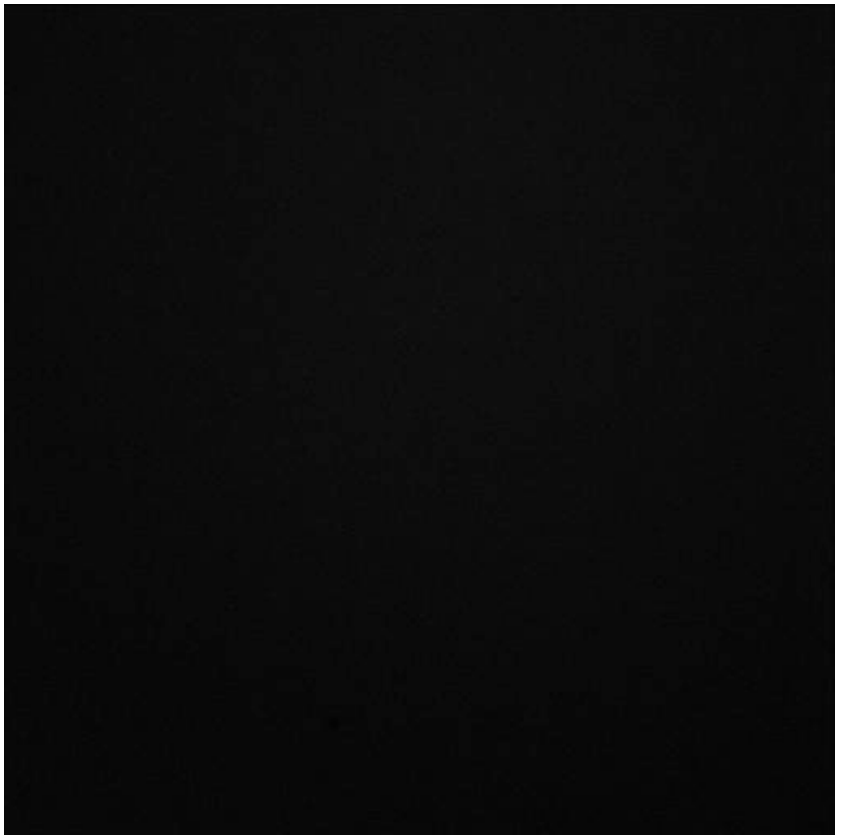


A photoactivation system can control the protein translocation to the nucleus and gene expressions in mammalian cells

Controlled protein shuttling between cytosol and nucleus

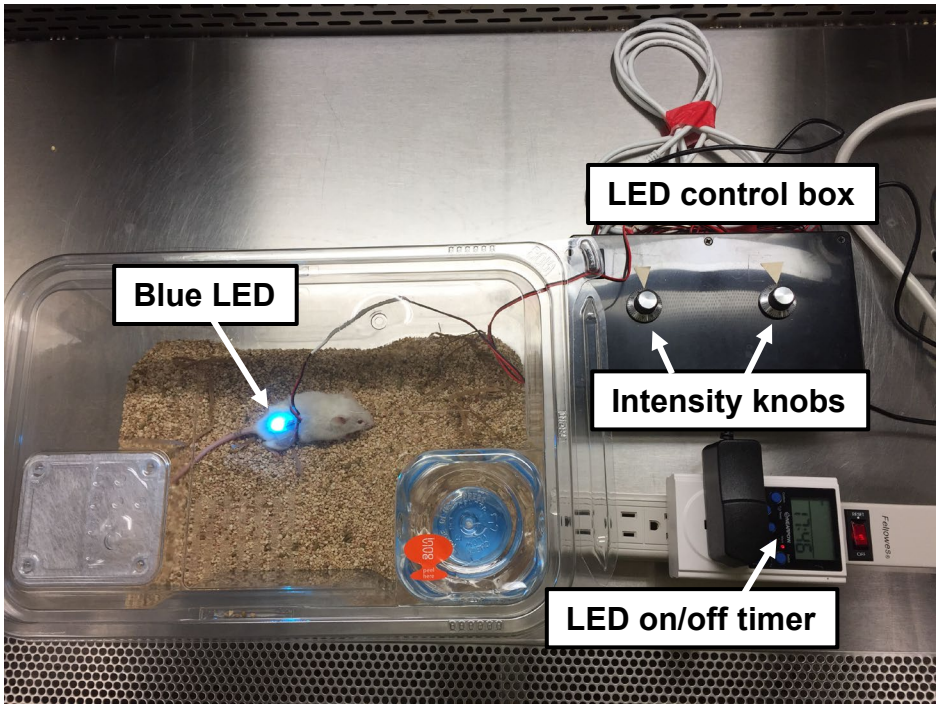


Controlled gene expression



Photoactivation can control the CAR expression in PBMCs for Tumor Eradication in mice

a



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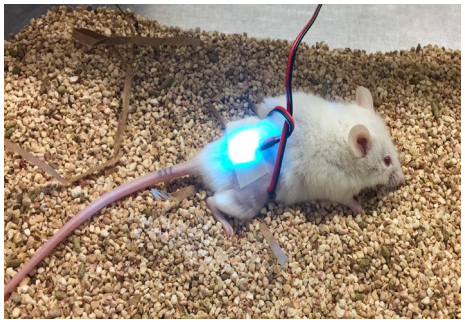

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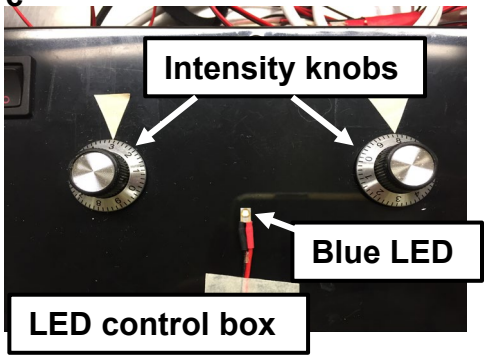

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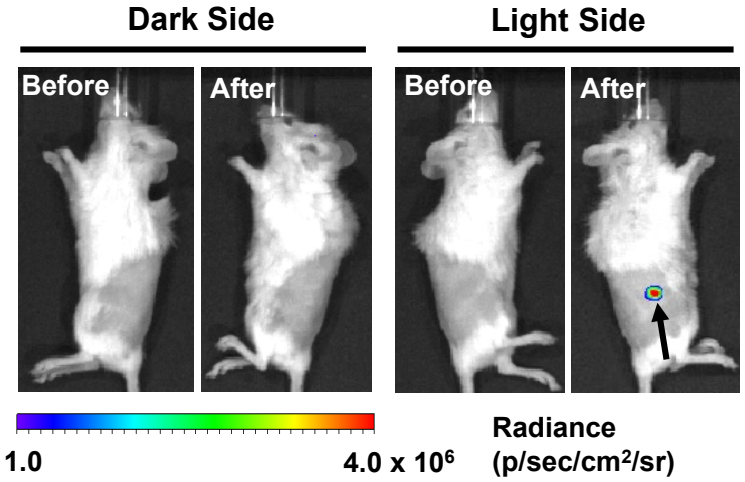

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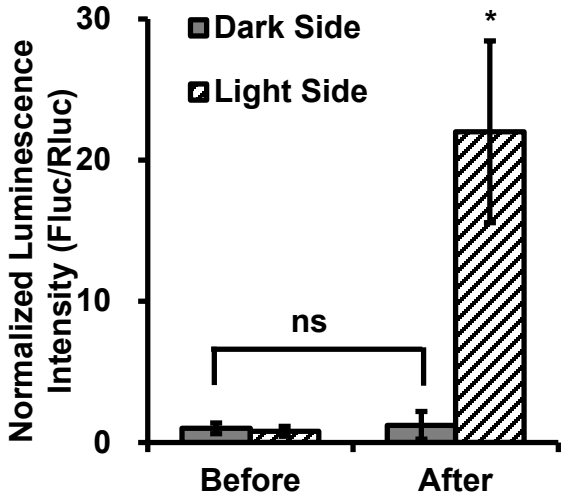
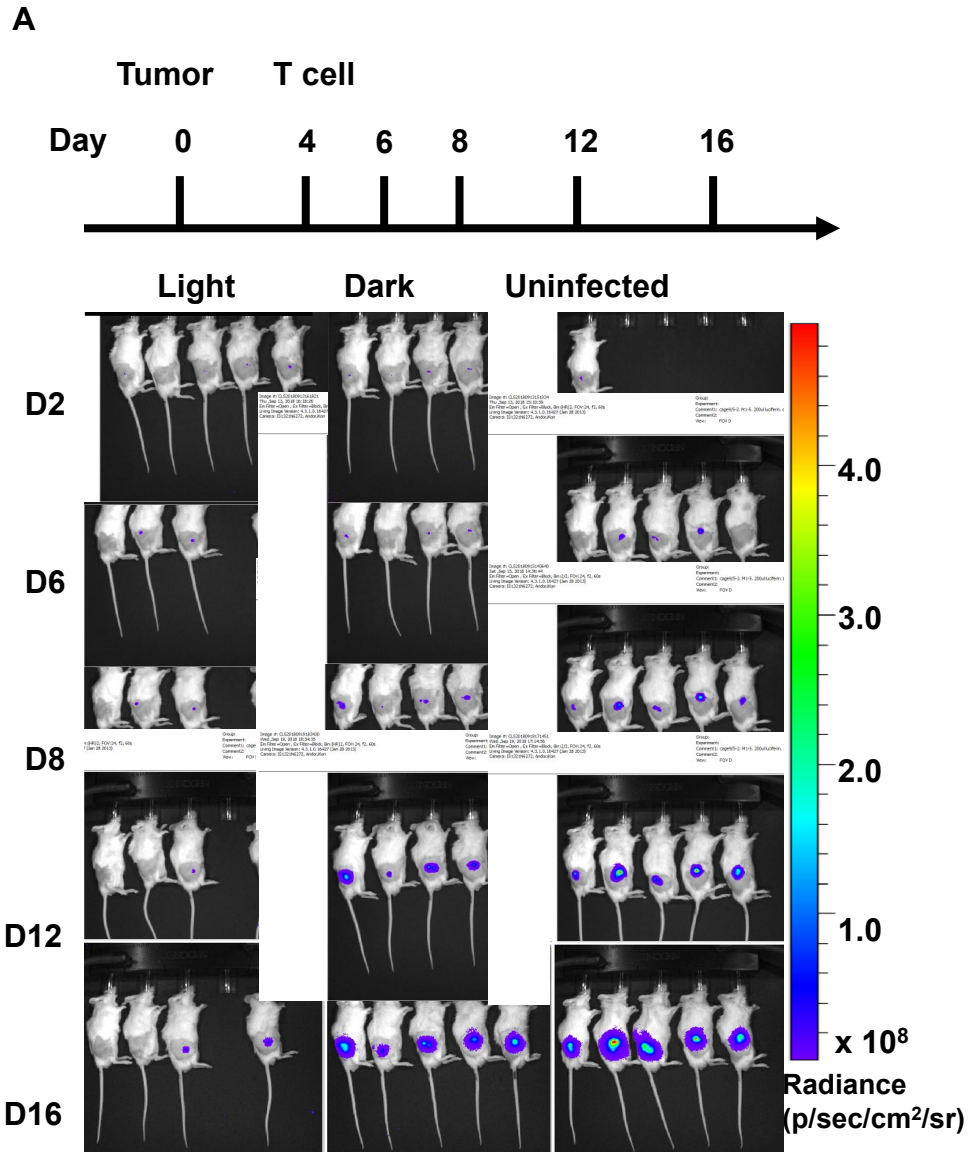
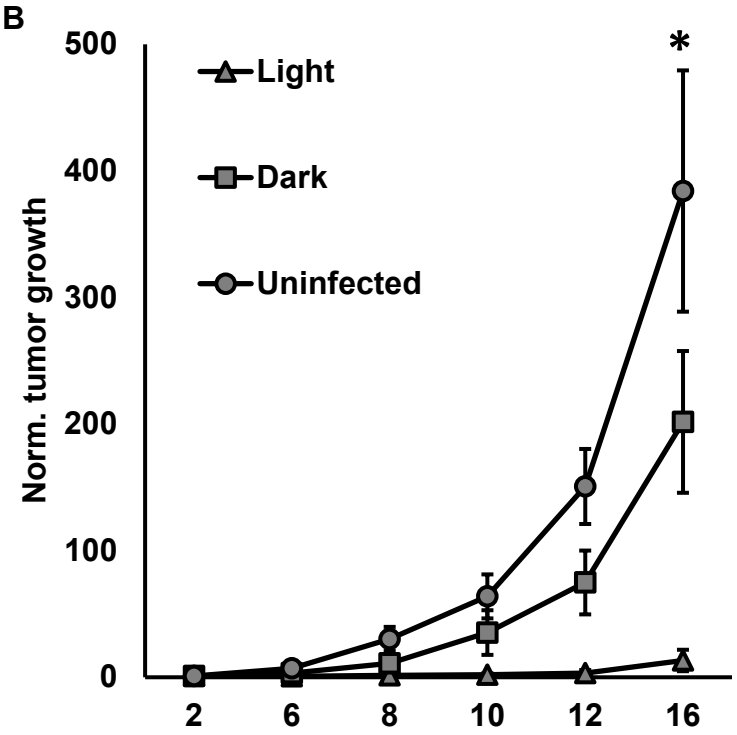


Photoactivation can control the CAR expression in PBMCs for Tumor Eradication in mice





Huang Z. Wu Y. et al Science Advances, 2020

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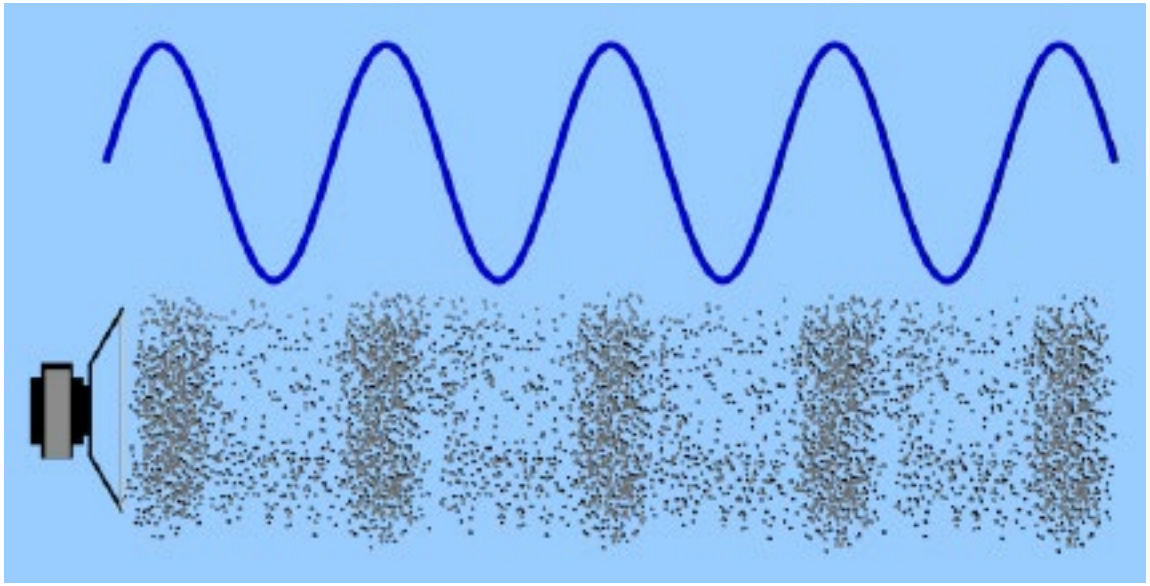
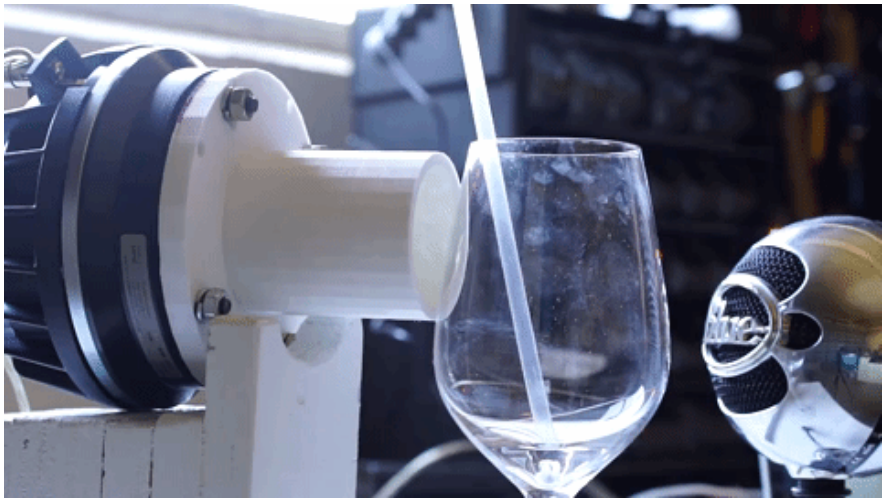
Remote and Non-invasive Control of Cells with ultrasound

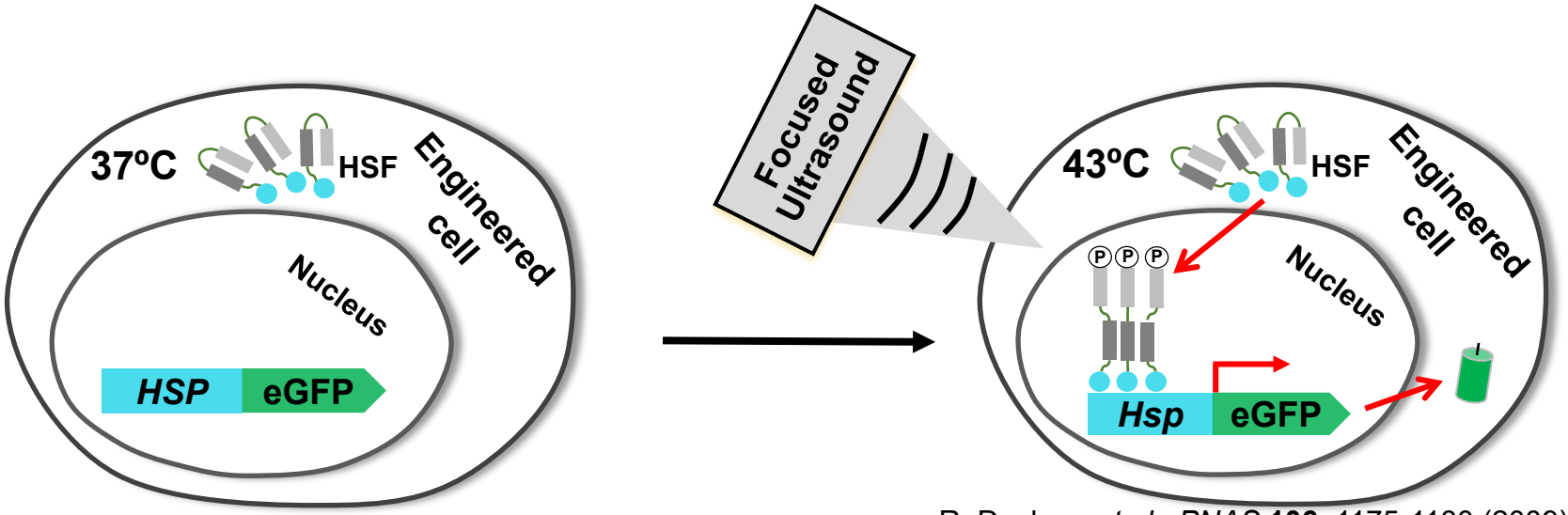
Ultrasound signals are Mechanical and Longitudinal waves that can transfer a distance.



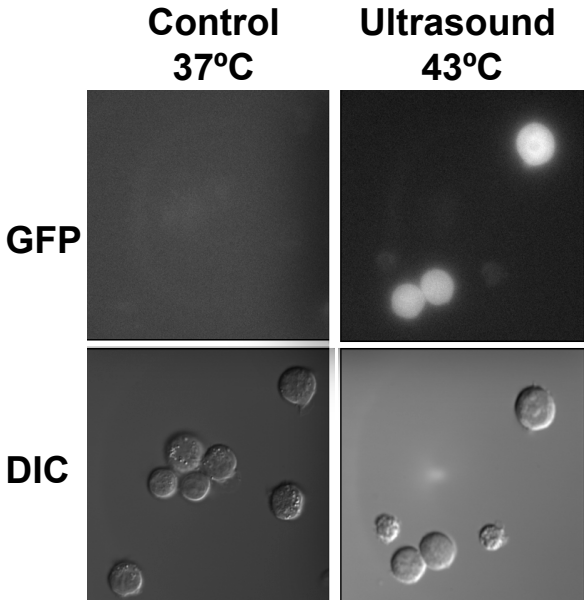
Sound waves can break glass

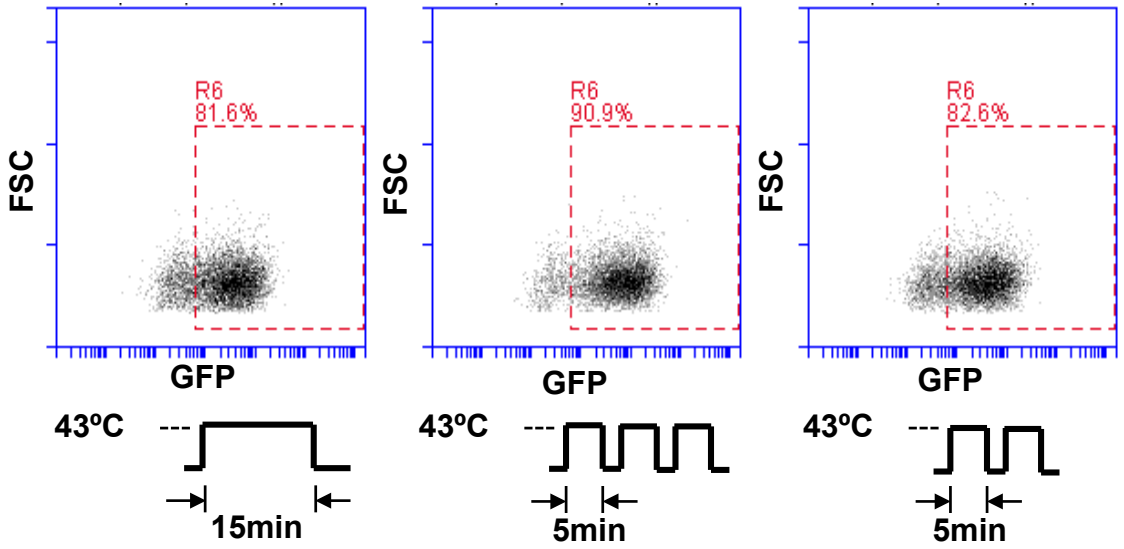


Ultrasound-controllable Gene Activation via short pulsed heat shocks



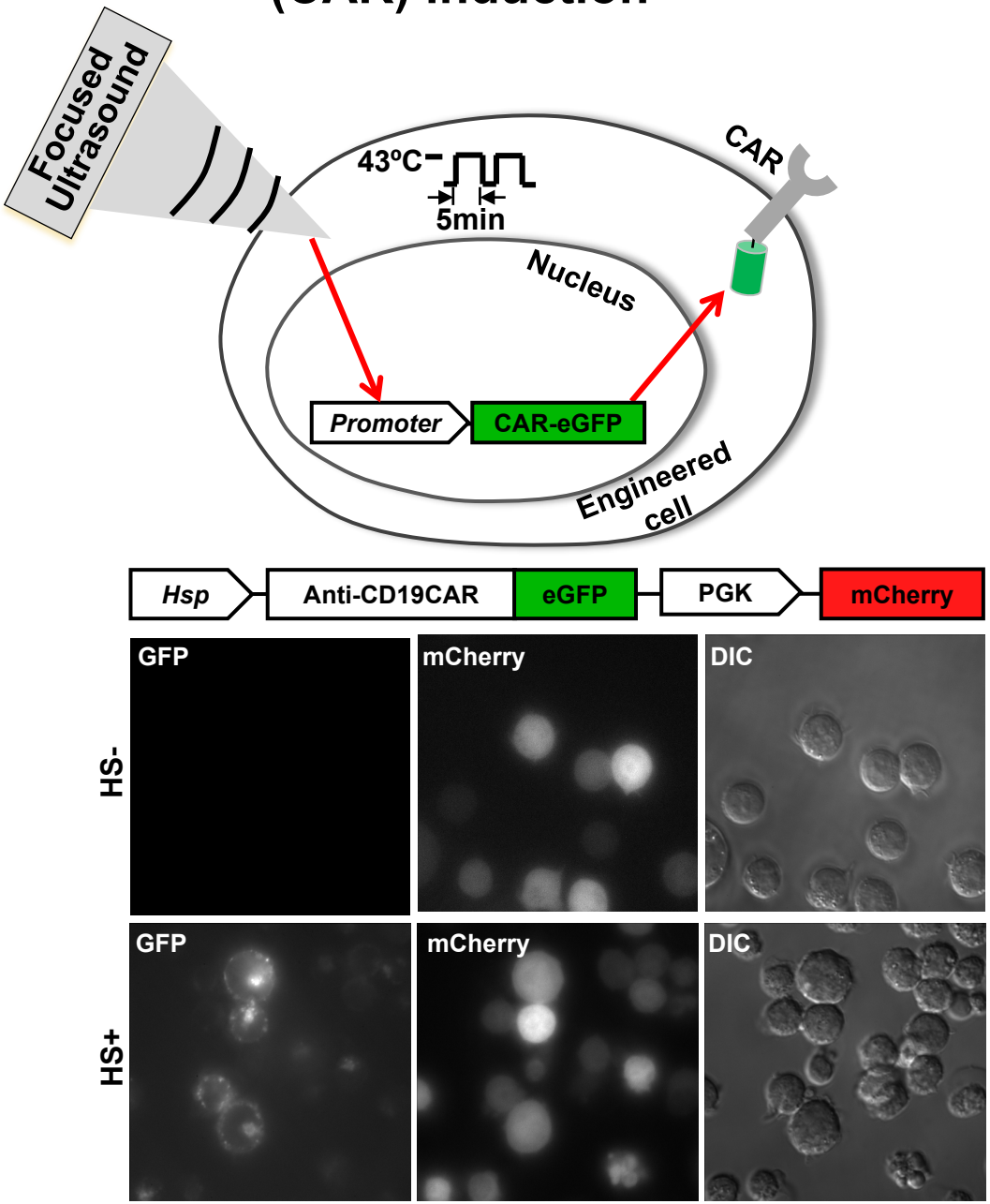
R. Deckers *et al.*, *PNAS* **106**, 1175-1180 (2009); E. Guilhon *et al.*, *Mol Imaging* **2**, 11-17 (2003).



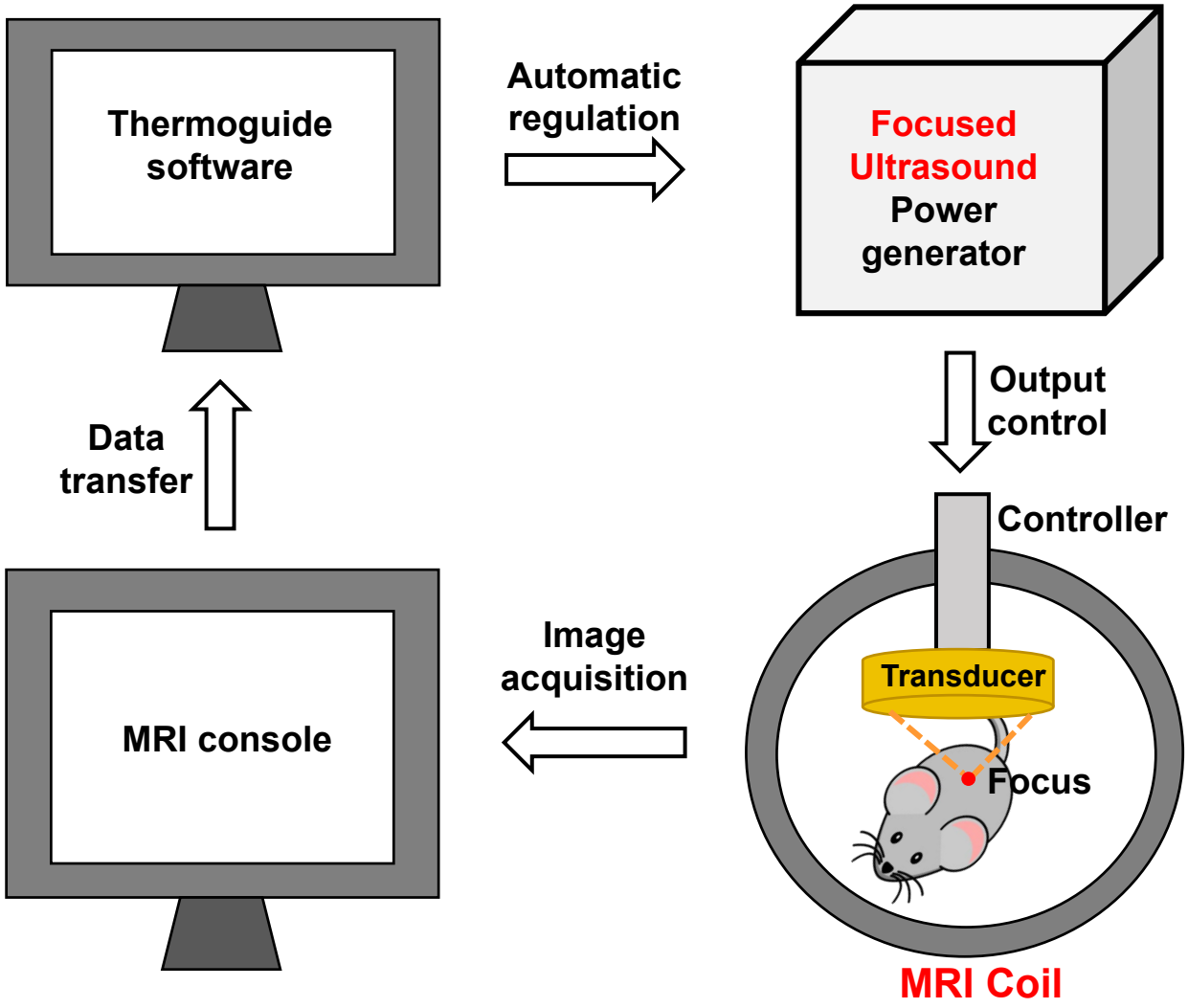


Short pulsed ultrasound stimulation is sufficient for gene activation.

Short Pulsed Heat stimulation is sufficient for chimeric antigen receptor (CAR) induction



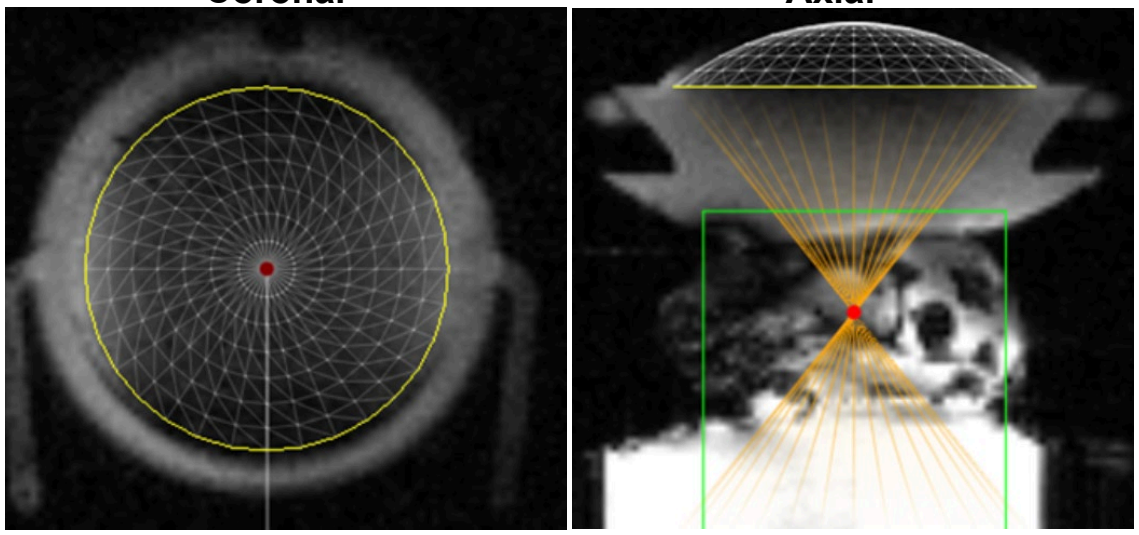
MRI-Guided Ultrasound Stimulation *in vivo*



We established a system for MRI-guided focused ultrasound stimulation *in vivo*

MRI-Guided Ultrasound Stimulation *in vivo*

A



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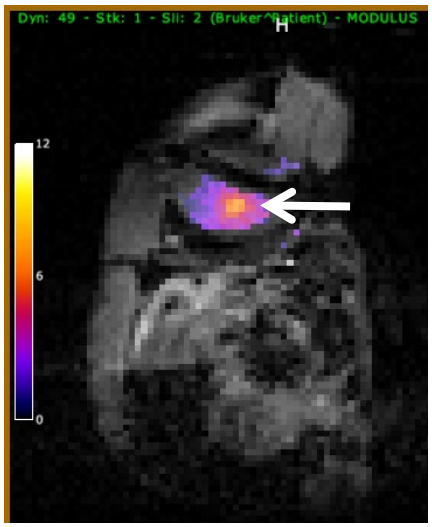
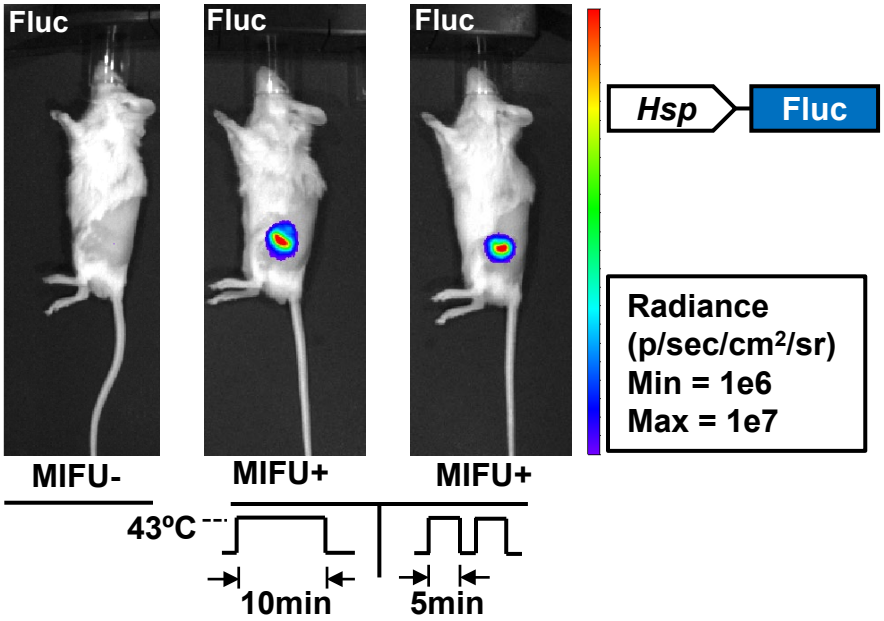


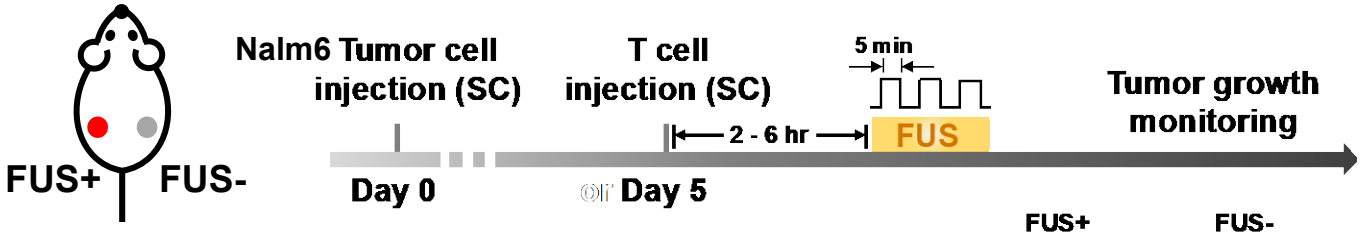
Temperature heat map

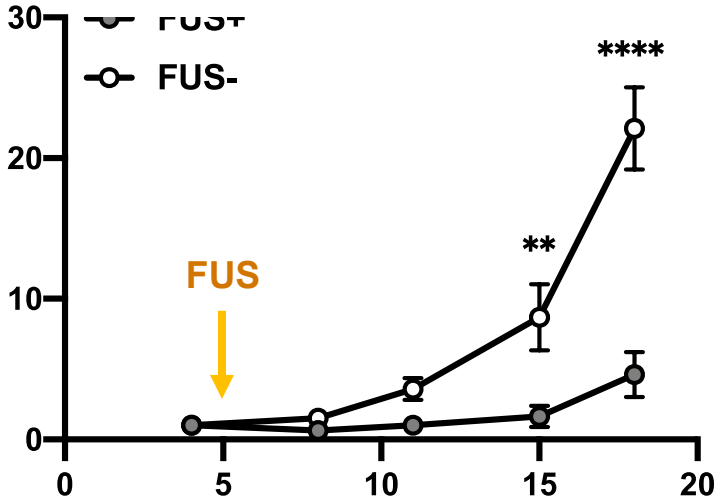
C

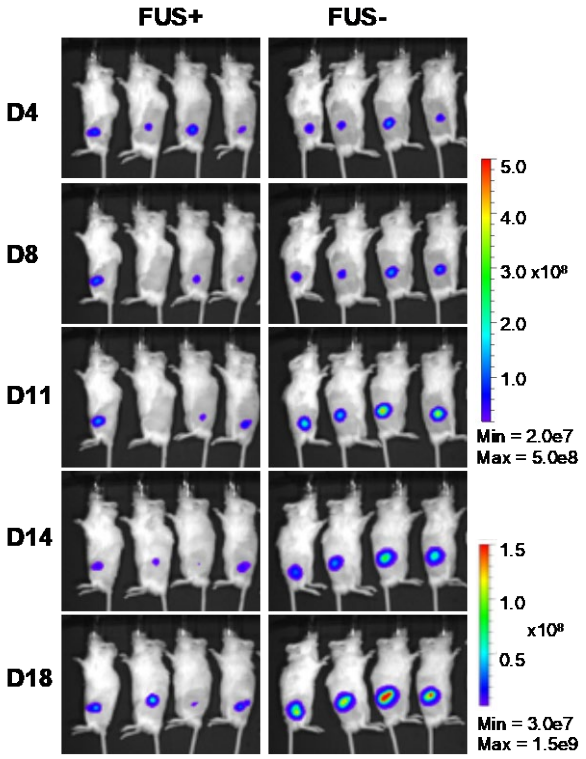


This MRI-guided ultrasound stimulation can activate gene expressions *in vivo* at specific local regions.

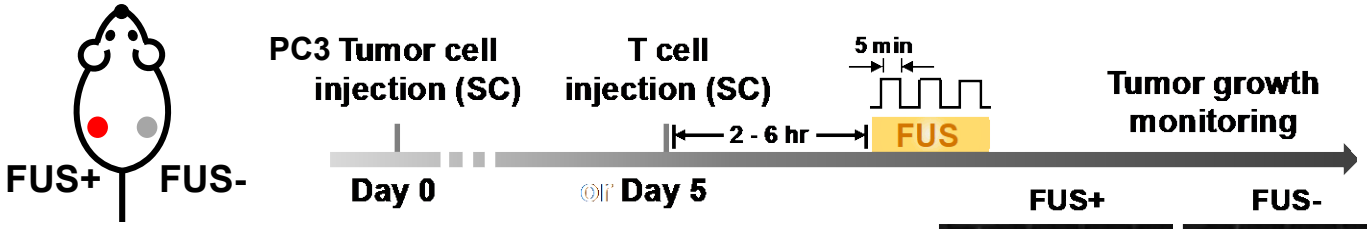
MRI-guided FUS-inducible CAR T cells *in vivo for lymphoma tumors*

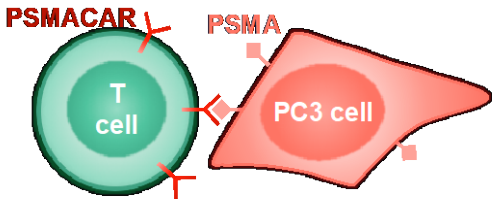


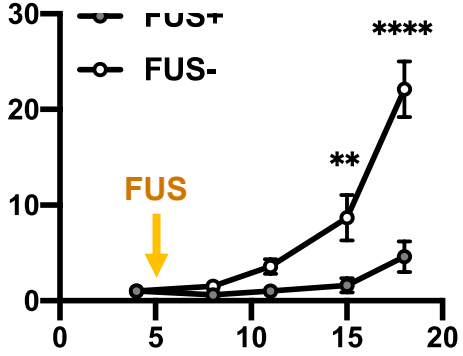


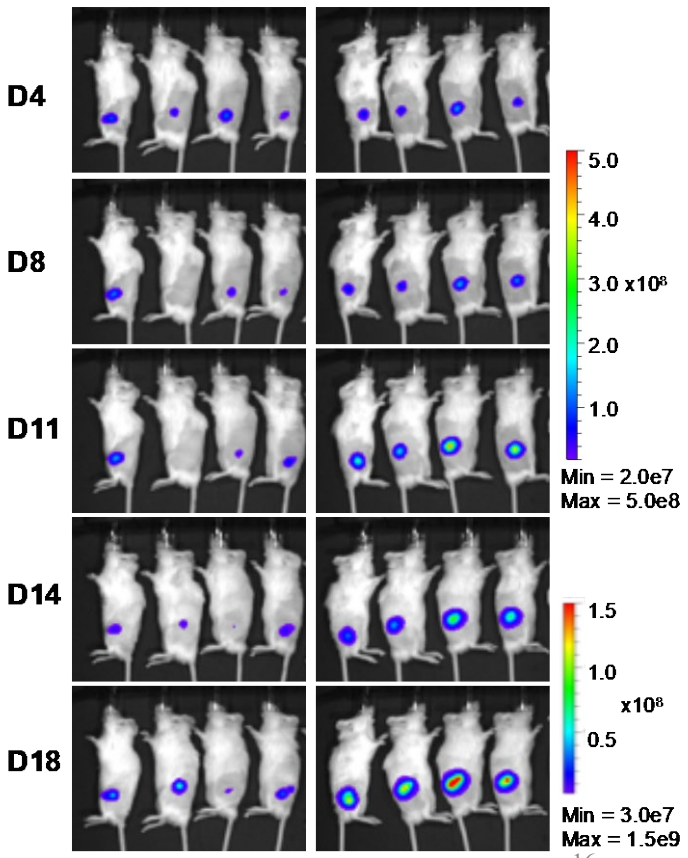


MRI-guided FUS-inducible CAR T cells *in vivo for prostate cancer*





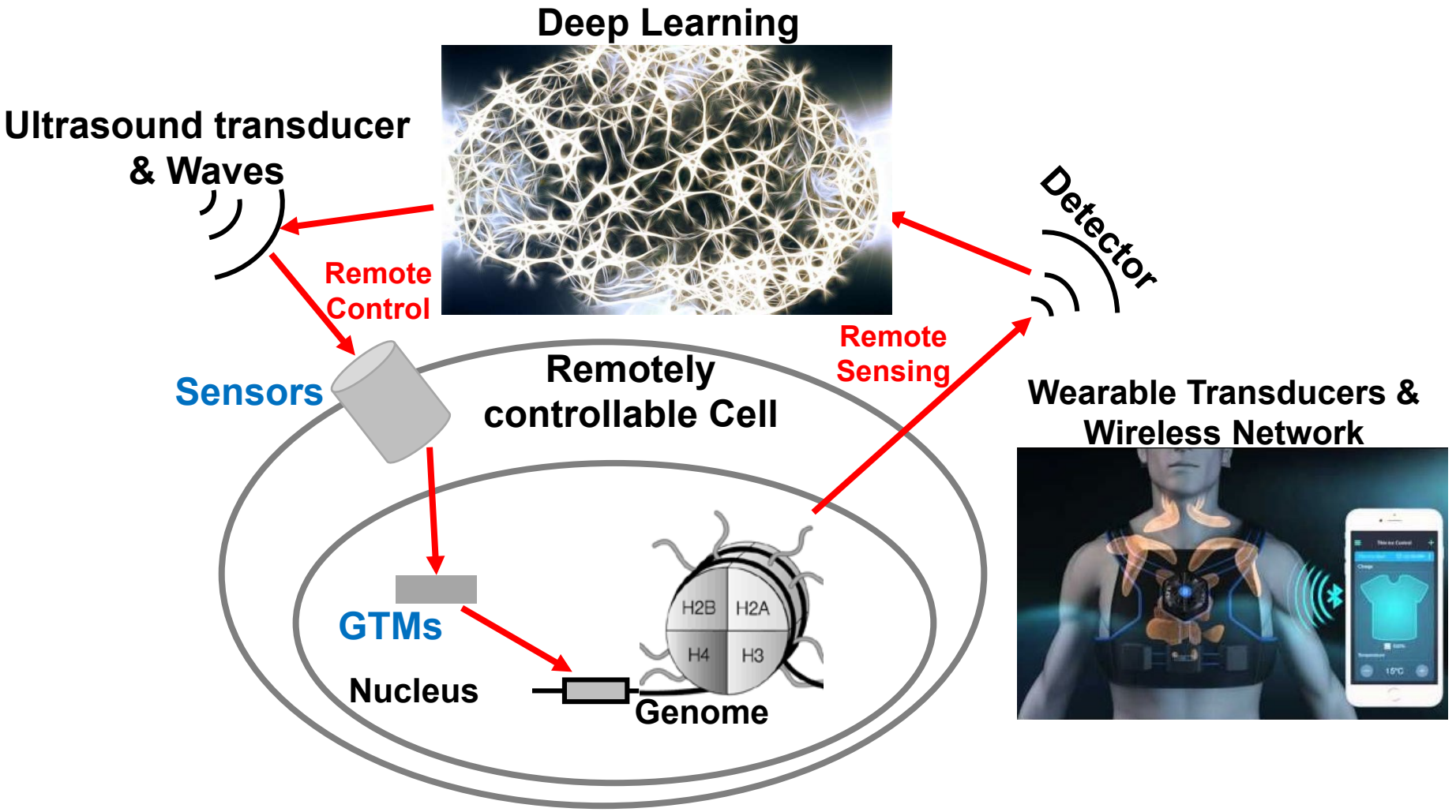




Wu Y. et al in revision

Looking Forward

Develop acoustogenetics to remotely and non-invasively control/edit genomics and epigenetics in live animals, gaining molecular insights and guiding therapeutics



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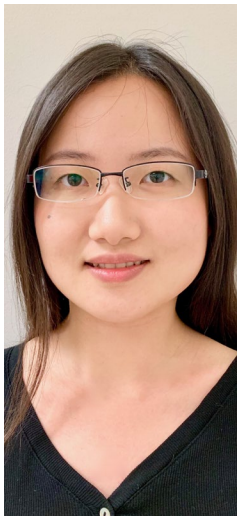

Collaborators:

Michael Berns, Shu Chien, Enfu Hui, Song Li, Willis Li, Tom Liu, Bing Ren, Michel Sadelain, Kirk Shung, Alex Strongin, Wei Wang, Xiang-Lei Yang, Jin Zhang, Yunde Zhao, Cheng Zhu

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